A 39-Year-Old Female Patient With Metastatic Rectal Cancer Develops Thrombocytopenia

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CASE REPORT

Dr. Dbouk: A 39-year-old woman presented with rectal bleeding of 2 months' duration. Investigations revealed adenocarcinoma of the rectum with liver metastases. The patient was a nonsmoker with no relevant medical comorbidities and no family history of malignancy. She underwent palliative chemotherapy with FOLFOX4 via intravenous infusion (oxaliplatin 85 mg/m^2, 2 hours; calcium folinate mg/m^2, 2 hours; 5-fluorouracil [5-FU], 400 mg/m^2 bolus, followed by 2400 mg/m^2, 46 hours, at fortnightly intervals; and bevacizumab, 5 mg/m^2).

Dr. Abou-Alfa: Dr. Dbouk, please tell us about the mechanism of action and adverse effects of oxaliplatin.

Dr. Dbouk: Oxaliplatin is a third-generation, platinum-containing, anticancer drug with established effectiveness in colorectal cancer (CRC).[1] It is a water-soluble compound with a diaminocyclohexane platinum carrier ligand. Oxaliplatin induces the formation of platinated DNA adducts, inhibiting DNA synthesis and repair and finally causing apoptosis. The diaminocyclohexane platinum carrier ligand is more effective on nucleic acid metabolism, with less or similar toxicity than the original platinum compound cisplatin.[2] Common adverse effects associated with the administration of oxaliplatin in combination with 5FU and calcium folinate in the setting of metastatic disease include nausea (all grades, 69.9%; grade 3, 8%; and grade 4, <1%), vomiting (all grades, 49%; grade 3, 6%; and grade 4, 1%), diarrhea (all grades, 60.8%; grade 3, 9%; and grade, 4 2%), and mucositis/stomatitis (all grades, 39.9%; grade, 3, 4%; and grade 4, <1%). Myelosuppression may be noted as well: anemia (all grades, 82.2%; grade 3, 3%; and grade 4, <1%), thrombocytopenia (all grades, 71.6%; grade 3, 4%; and grade, 4 <1%), and neutropenia (all grades, 71.4%; grade, 3 28%; and grade, 4 14%).[3] The dose-limiting toxicity of oxaliplatin is a sensory neuropathy with paresthesias and dysesthesias (76%). Neuropathy can be acute and reversible (all grades, 65%, and grades 3/4, 5%) or persistent (all grades, 43%, grades 3/4, 3%).[4,5] Hypersensitivity and anaphylactoid reactions may be observed. Ten to 15% of patients receiving oxaliplatin develop hypersensitivity reactions, often after multiple cycles of the FOLFOX regimen.[6] Such patients can undergo a desensitization protocol that may be effective and help them to continue to receive the drug.[7]

Dr. Abou-Alfa: Thank you Dr. Dbouk. Dr. Lee, please tell us about the mechanism of action and adverse effects of bevacizumab.

Dr. Lee: Bevacizumab is a recombinant, humanized monoclonal antibody that binds to and neutralizes vascular endothelial growth factor (VEGF), preventing its association with the endothelial receptors Flt-1 and KDR. VEGF binding initiates angiogenesis (endothelial proliferation and the formation of new blood vessels). The inhibition of microvascular growth is believed to retard the growth of all tissues (including metastatic tissue). Common adverse effects include hypertension (all grades, up to 42%, grades 3/4, 0.4–17.9%), bleeding (grades 3–5, 0.4–6.5%), proteinuria (all grades, 38%; grade 3, 8.1%, grade 4, up to 1.4%), and venous thrombosis (all grades, up to 17%; grades 3–5, up to 7.8%).[8,9] May I ask how you defined the goals of therapy for CRC?

Dr. Mukherji: The goals of systemic therapy for metastatic (m)CRC include palliation of symptoms, prolongation of life, and, in selected cases, tumor regression to facilitate surgical resection of metastases. The median survival of patients with mCRC has improved during the past decade, from less than 1 year, with only 5FU-based therapy, to approximately 2 years, with multiagent, systemic therapy.[10]

Dr. Abou-Alfa: Thank you Dr. Mukherji. I believe we have discussed potential curative approaches for mCRC at this conference in the past.[11] Dr. Dbouk, please tell us how the patient did.

Dr. Dbouk: After 4 cycles of FOLFOX+bevacizumab, computed tomography (CT) revealed a partial response, as per RECIST (Response Evaluation Criteria in Solid Tumors) 1.1[12] and the serum carcinoembryonic antigen (CEA) level decreased from 178.9–11.6 to 0–7 ng/ml. Because of the partial response to systemic treatment, local control of the symptomatic rectal disease was considered important. The patient commenced capecitabine chemotherapy with concurrent radiation to the rectum followed by laparoscopic low anterior resection. Histopathologic examination of the resected specimen revealed scattered microscopic foci of residual adenocarcinoma at the primary tumor site. Proximal and distal margins were free of tumor, and 5 benign lymph nodes were identified. The patient recovered well after surgery, but disease progression occurred in the liver within 2 months. The patient was treated with 3 cycles of FOLFOX without bevacizumab, since surgery was being considered because of the partial RECIST 1.1 response and normalization of CEA. The patient was referred for consideration of resection of liver metastasis.

Dr. O'Reilly: Dr. Haydar, what would be the best imaging modality to determine resectability?

Table 1 Platelet count before and after treatment, investigations, and management during FOLFOX chemotherapy courses 13–17

Course	Platelets/mm^3		Onset (hours)	Symptoms	Investigations	Treatment	Results
	Before	After					
13	174,000	91,000	8	No	No	No	Recovery
14	217,000	49,000	12	No	PT, PTT D-dimer, fibrinogen were normal	No	Recovery
15	231,000	12,000	12	Minimal bleeding at the site of colostomy	PT, PTT D-dimer, fibrinogen were normal	No	Recovery
16	210,000	9,000	12	Minimal epistaxis	PT, PTT were normal	Platelet transfusion	Recovery
17	258,000	37,000	1	Minimal purpura	PT, PTT, fibrinogen, D-dimer, bone marrow aspirate, LDH, Coombs, platelet antibodies	No	Recovery
		17,000	12				
		25,000	24				

PT, prothrombin time; PTT, partial thromboplastin time.

Dr. Haydar: In the neoadjuvant setting, magnetic resonance imaging (MRI) and CT can both be used. Diagnostic accuracy of [18F]-fluorodeoxyglucose–positron emission tomography (FDG-PET) and PET-CT is strongly affected by chemotherapy.[13] PET within 4 weeks of chemotherapy is not a useful test for evaluation of colorectal hepatic metastases. The high rate of false-negative results is most likely due to the metabolic inhibition caused by chemotherapeutic drugs.[14]

Dr. Dbouk: The patient underwent exploratory laparoscopy that revealed lesions in segments III, IV, VII, and VIII of the liver that had not been visualized on preoperative PET-CT. Biopsies were taken, and no resection was performed; pathology showed adenocarcinoma consistent with metastasis from CRC. Palliative chemotherapy with FOLFOX4+bevacizumab was resumed, since surgical resection was not possible.

Dr. Saltz: That is quite a bit of oxaliplatin. How has the patient done so far?

Dr. Dbouk: Before the 12th course of therapy, a complete blood count showed normal results: hemoglobin, 11.3 g/dl (reference range, 12–16 g/dl), and platelets, 174,000/mm^3 (reference range, 150,000–400,000/mm^3). The patient was admitted, and chemotherapy was administered after adequate premedication, including antihistamines and steroids. Eight hours after the end of oxaliplatin infusion, a complete blood count was repeated as a routine test for inpatients. The platelet level had dropped to 91,000/mm^3, with no significant changes in the hemoglobin level or absolute neutrophil count (ANC). The patient felt well, and no interventions were indicated. However, this finding was noted and followed up after each subsequent cycle of treatment (**Table 1).** During the 17th course, a complete blood count on admission showed an appropriate hemoglobin of 10 g/dl, a platelet count of 258,000/mm^3, and an absolute neutrophil count of 5,312/mm^3. Oxaliplatin was administered over the planned 2 hours, with subsequent development of purpura on the upper extremities. A complete blood count was obtained and showed a platelet count of 37,000/mm^3.

Dr. Mentha: That is quite troubling. Did you perform any further testing?

Dr. Dbouk: Fibrinogen, prothrombin time, bilirubin (total and direct), indirect Coomb's test, haptoglobin, and blood film were all normal: lactate dehydrogenase (LDH), 592 IU/L (reference range, 110–265 IU/L); D-dimer, 1113 ng/mL (reference, <255 ng/mL); and direct Coomb's, positive/IgG (2+).

Dr. Abou-Alfa: Dr. Mentha, please help us explain all of this.

Dr. Mentha: Was an anti-platelet antibodies test done?

Dr. Dbouk: Testing for anti-platelet antibodies showed an increase in fixed IgG on the platelet surface without circulating complex immune fixation in the presence of auto-antibodies directed against glycoprotein (GP) complexes Ia, IIa, IIIa, and Ib, Ix.

Dr. Mentha: These results show drug binding to the platelet surface that can form a new epitope or cause the exposure of a neoepitope. GP Ib/V/IX, and GP IIb/IIIa are most frequently involved in drug binding, which leads to the formation of new epitopes that appear to be very specific for each different drug.[15,16] The development of drug-dependent anti-platelet antibodies may cause accelerated platelet clearance in vivo and induce severe thrombocytopenia. Laboratory assays are capable of demonstrating the presence of drug-dependent anti-platelet antibodies. These assays are not generally available in routine hospital laboratories and are not essential for making the clinical diagnosis of drug-induced thrombocytopenia (DITP) at the time of initial presentation. Flow cytometry–based methods to identify drug-dependent platelet antibodies are the most commonly used.[17] Documentation of drug-dependent anti-platelet antibodies is helpful in confirming the diagnosis of DITP and supports the recommendation that the patient never again be exposed to this agent. However, negative in vitro test results may be obtained from patients with a clinical course suggestive of DITP, even when several different assays are used.[18] Potential causes of a false-negative result include characteristics of the stock drug used in testing and the antibody binding mediated by a metabolite, rather than the primary compound.

Dr. O'Reilly: Are there any criteria that are required for suspecting the presence of DITP?

Dr. Mentha: Three criteria are necessary.[19] First, administration of the implicated drug should be temporally associated with the onset

of thrombocytopenia, the latter usually occurring within 1 week of using a drug for the first time, or earlier when the patient has been exposed to the agent previously. Second, the platelet count nadir should be less than 30,000/mm^3. Finally, there should be no plausible alternative explanation for the thrombocytopenia. Other diagnoses worth considering include classic idiopathic thrombocytopenia, disseminated intravascular coagulation, myelosuppression secondary to cytotoxic drugs, and thrombocytopenia secondary to sepsis.

Dr. Abou-Alfa: So in the current case, one can confirm the presence of DITP. Any further confirmation needed?

Dr. Mentha: The gold-standard confirmation of DITP is observing that the thrombocytopenia disappears when a single potentially causative drug is stopped and reappears when that drug is reintroduced. The latter maneuver is potentially dangerous and is not recommended, since the second episode of thrombocytopenia may lead to severe, potentially fatal bleeding. Laboratory testing for DITP is not readily available in most centers, but documentation of drug-dependent anti-platelet antibodies in a reference laboratory can help confirm the diagnosis.

Dr. Lee: What are the mechanisms of oxaliplatin-induced thrombocytopenia?

Dr. Shamseddine: Mild bone marrow suppression, similar to that of other platinum-based compounds, is the main cause of oxaliplatin-induced thrombocytopenia. However, novel mechanisms of oxaliplatin-induced thrombocytopenia have emerged that may be associated with a different clinical presentations and may even need different approaches.[20,21] These novel mechanisms include an immune-dependent mechanism and splenic sequestration of platelets due to portal hypertension related to sinusoidal injury.

Dr. Abou-Alfa: Dr. Saltz, based on your experience, please help in summing up the clinical manifestations and treatment of oxaliplatin-induced immune thrombocytopenia.

Dr. Saltz: The usual presentation is an acute and severe drop in platelet count, leading to clinical symptoms of bleeding or bruising within a few hours, but sometimes in up to 48 hours, after the administration of a treatment cycle of oxaliplatin. The nadir platelet count can be as low as 2 mm^3. This complication most commonly affects female patients with advanced CRC and prior oxaliplatin exposure, usually occurring during retreatments. In the majority of cases, this complication arises after a total of at least 12 cycles of oxaliplatin. In some cases, thrombocytopenia can follow the onset of hypersensitivity reactions, such as skin rash, pruritus, chills, and bronchospasm.[22]

Dr. Abou-Alfa: Is there any treatment?

Dr. Mentha: There is no specific treatment for most patients with oxaliplatin-induced immune thrombocytopenia. Platelet counts usually recover a few days after discontinuation of the drug, which is the main therapeutic maneuver. The patient should not receive oxaliplatin again and should carry a medical alert bracelet documenting this instance of drug sensitivity, since susceptibility to the offending agent usually persists indefinitely.[20] For patients with major bleeding, appropriate hematologic support, including platelet transfusions, may be necessary to keep the platelet count at a safe level. A post-transfusion platelet increase should be checked approximately 15 minutes to 1 hour after the infusion to ensure that a satisfactory increment has occurred. Given that the platelets are cleared through an immune mechanism, the response to allogeneic platelets may be unsatisfactory. The value of steroids and intravenous immune globulins in this context is uncertain. Those modalities should be considered if the patient is actively bleeding or considered at high risk of major bleeding. Recovery is usually fast and complete after discontinuation of the offending drug.

Dr. Mukherji: Based on the above, oxaliplatin was discontinued, and the patient developed thrombocytopenia after previous exposure to several cycles of oxaliplatin, suggesting an immune-mediated mechanism driven by repeated drug exposure. The diagnosis of acute immune-mediated thrombocytopenia due to oxaliplatin was made. Therefore, chemotherapy was changed to FOLFIRI (5-fluorouracil, leucovorin, irinotecan)+bevacizumab.

Dr. Shamseddine: In summary, this is a case of a young patient presenting with metastatic rectal cancer, treated with multimodality therapy, including systemic chemotherapy, chemoradiotherapy, and surgery. Oxaliplatin-induced thrombocytopenia is a rare complication of oxaliplatin therapy usually presenting with a sudden and isolated drop in platelet counts minutes to hours after administration of oxaliplatin. Female patients with advanced CRC and prior oxaliplatin exposure are more likely to develop this complication. Prompt immunologic testing documenting oxaliplatin-mediated platelet destruction leads to a definitive diagnosis. Platelets counts will improve after discontinuation of treatment, but platelet transfusions may be necessary during the acute phase. Other measures, such as corticoid or immunoglobulin administration, are controversial. Patients with documented oxaliplatin-induced thrombocytopenia should not be rechallenged with oxaliplatin. Healthcare professionals should be aware of the risk of rapid-onset, severe, life-threatening thrombocytopenia and possible hemolysis in patients who have had several previous cycles of oxaliplatin.

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